

# Aseptic Meningitis Epidemic Involving ECHO 4 and Coxsackie B5 Viruses

HOWARD J. GARBER, M.D., THOMAS H. GLICK, M.D., J. MEHSEN JOSEPH, Ph.D.,  
HERBERT DUPONT, M.D., and STEFAN EICHLER

**T**HE FIRST ATTEMPT to characterize aseptic meningitis as a distinct entity was made by Wallgren (1) in 1925. Although his criteria are still useful today, improved laboratory diagnostic techniques now make it possible to demonstrate that what he originally assumed to be a single disease may occur in the course of infection due to a number of different etiological agents.

The enteroviruses, other than the poliovirus, which have been associated with the aseptic meningitis syndrome in epidemic form include ECHO 4, 6, 9, 11, 16, and 30 (2), as well as Coxsackie A2, 4, 7, 9, 10, 16, and B1-B6 (3). The other types most frequently implicated, in addition to ECHO 9, are ECHO 4 and Coxsackie B5. The first reported outbreak of aseptic meningitis associated with ECHO 4 occurred in Marshalltown, Iowa, in 1955 (4, 5); the first reported

epidemic of aseptic meningitis associated with Coxsackie B5 was in Cerro Gordo County, Iowa, in 1956 (6). In a search of the U.S. literature, however, we found no reports of a well-defined epidemic of aseptic meningitis in which two enteroviruses, excluding poliovirus, played major etiological roles. Such an epidemic did occur in Baltimore, Md., in 1967.

Baltimore, in central Maryland, is surrounded by, but is politically distinct from, Baltimore County. According to estimates by the bureau of vital statistics of the Baltimore City Health Department, the population as of July 1, 1966, was 914,000. Approximately 41 percent of the population is nonwhite. Thirty-nine percent of the inhabitants are less than 20 years old.

In 1967, epidemiologists of the Maryland State Department of Health, after being notified of an increased number of cases of aseptic meningitis in one Baltimore hospital, undertook a telephone survey of hospitals and offices of selected pediatricians to assess the possibility of an outbreak in the city. When an increased incidence was confirmed by a number of these sources, letters were sent to all Maryland physicians alerting them to the pattern of symptoms and the laboratory results. Specimens of blood and spinal fluid, stool or rectal swabs, and throat swabs or washings were requested for laboratory study.

Most of the reported cases were among the

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*Dr. Garber, Dr. Glick, and Dr. Dupont are epidemic intelligence service officers with the National Communicable Disease Center, Public Health Service. Dr. Garber is assigned to the Maryland State Department of Health in Baltimore, Dr. Glick to NCDC in Atlanta, Ga., and Dr. Dupont to the University of Maryland School of Medicine in Baltimore. Dr. Joseph is assistant director, bureau of laboratories, Maryland State Department of Health, and Mr. Eichler is head of the virus isolation laboratory of that bureau.*

patients of teaching hospitals and clinics; only a small percentage of the cases were reported by private physicians. We included in our study only those cases occurring between July 1 and November 1, 1967, in which the reported clinical and laboratory observations were consistent with aseptic meningitis. On this basis, 202 cases were accepted. All met the following criteria: (a) acute onset of illness, (b) headache or fever, with or without meningeal signs, (c) spinal fluid pleocytosis of 5 or more white blood cells per cubic millimeter, (d) short duration of illness without major alteration of consciousness, localizing neurological signs, or neurological residua, and (e) no evidence of other viral illnesses or bacterial meningitis.

Specimens for viral isolation were obtained from 115 patients (56.9 percent). Stool, throat, and cerebrospinal fluid specimens collected from the patients were either cultured directly or kept frozen at  $-65^{\circ}\text{C}$ . until examined in the laboratory. Viral isolation was attempted in Rhesus monkey kidney and HEp-2 tissue cell cultures. Most specimen materials were inoculated into suckling mice. Viruses which were isolated were identified by the neutralization test, in which prototype hyperimmune serums and 100 TCID<sub>50</sub> of virus were used (?). The National Communicable Disease Center, Public Health Service,

supplied the antiserum, except Coxsackie B5 antiserum, which was obtained from Microbiological Associates, Bethesda, Md.

Serologic studies were performed on the patients' serums by the neutralization test with antigens obtained from the National Communicable Disease Center. Except for ECHO 4, prototype viruses were used as antigens in the test for ECHO and Coxsackie viruses. In the test for ECHO 4, antigen of the Dutoit strain was used.

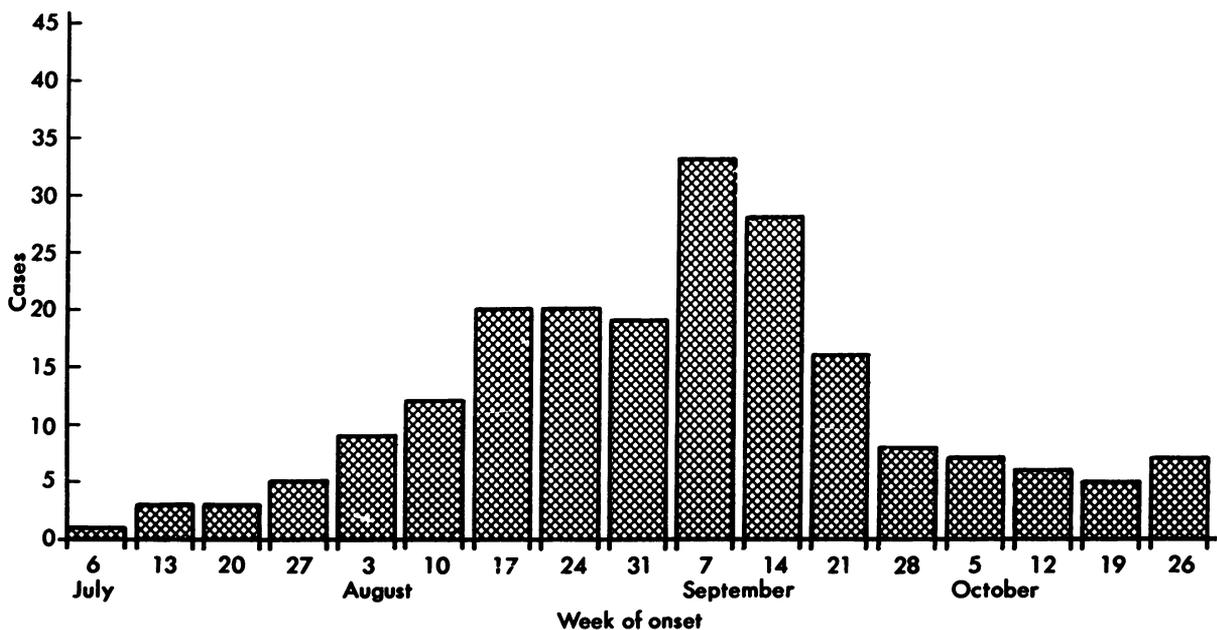
#### Description of Epidemic

The 202 cases of aseptic meningitis reported to the Baltimore City Health Department in the 4 months July through October 1967 were 40 times as many as were reported in the comparable period in 1966 and substantially more than in other recent years. Approximately 75 percent occurred in August and September; the epidemic peak was in the first 2 weeks of September (fig. 1).

There was no unusual clustering of cases geographically in the city; the earliest cases, however, occurred predominantly in the northeast section of the city. Later, cases also occurred in the eastern section with a spread to the west.

Of the 202 patients with aseptic meningitis, 67.8 percent were younger than 15 years (table

**Figure 1. Cases of aseptic meningitis, by week of onset, Baltimore, Md., July–October 1967**



**Table 1. Distribution of patients with aseptic meningitis by age group, race, and sex, Baltimore, Md., July-October 1967**

Age group (years)	Nonwhite		White		Total	
	Male	Female	Male	Female	Number	Percent
Less than 1	14	6	3	2	25	12.7
1-4	17	12	1	1	31	15.3
5-9	26	12	3	3	44	21.7
10-14	23	10	4	0	37	18.3
15-19	14	11	0	1	26	12.8
20-24	0	6	3	2	11	5.4
25 and over	6	12	5	5	28	13.8
Total	100	69	19	14	202	100.0

**Table 2. Aseptic meningitis attack rates per 100,000 population, Baltimore, Md., July-October 1967**

Age group (years)	Total			White			Nonwhite		
	Cases	Population	Attack rate	Cases	Population	Attack rate	Cases	Population	Attack rate
Less than 5	56	99,231	56.4	7	47,007	14.9	49	52,224	93.8
5-9	44	95,791	45.9	6	45,955	13.1	38	49,836	76.3
10-14	37	85,138	43.5	4	42,851	9.3	33	42,287	78.0
15-19	27	76,408	35.3	1	41,803	2.4	25	34,605	72.2
20-24	11	57,275	19.2	5	31,830	15.8	6	25,445	24.5
25 and over	28	500,157	5.6	10	328,068	3.1	18	172,089	10.5
Total	202	914,000	22.1	33	537,514	6.1	169	376,486	44.9

1). Males were affected 1.4 times more frequently than females, and the attack rate was seven times higher among nonwhites than among whites. The overall attack rate for the city was 22.1 per 100,000 persons (based on the estimated 1966 population). The attack rate was highest for children less than 5 years old (table 2). Of 178 households with cases, 12 had two cases. Since, in five of these households, the two cases occurred within 3 days of each other, some of these cases may have been co-primary. Unfortunately there was no opportunity to investigate household contacts of the persons with aseptic meningitis.

#### Clinical Features of Illness

Clinical histories from hospital records were obtained for all 202 patients (table 3). The onset of illness was usually abrupt. Fever equal to or greater than 99° F. orally occurred in 94.1 percent; the maximum mean recorded temperature was between 101 and 101.9° F. Headache, predominantly retrobulbar, was present in 83.2

percent; among the patients recorded as having no headache, 77.3 percent were under 2 years old. Gastrointestinal symptoms of nausea, vomiting, or anorexia were present in 74.2 percent of the patients studied. Stiff neck, as a sign or symptom, was found in 61.3 percent of the patients. Upper respiratory symptoms, photophobia, and myalgia did not contribute significantly to the clinical picture. There were no other important neurological complaints; the patients' reflexes were normal when tested, and no paralysis was noted. Rash was reported in only two children, siblings. No specimens were obtained from these two children for isolation; the children did not receive antibiotic therapy. No significant complications occurred during the course of illness in the cases reviewed.

The mean time between onset of symptoms and lumbar puncture was 2.3 days, with a range of less than 1 through 10. Spinal fluid pleocytosis of 10 or more white cells was present in 97.1 percent of the patients. The median number

of cells fell in the range of 100 to 499 per cubic millimeter (table 4). Predominant spinal fluid monocytosis was present in 68.3 percent of the 202 patients whose cases were reviewed. In general, the shorter the period between onset of symptoms and lumbar puncture, the higher the proportion of polymorphonuclear leukocytes in the spinal fluid. In 22 of the 26 patients in whom leukocytes comprised less than 50 percent of the white blood cell count on the first of two taps, lymphocytes predominated on the repeat tap.

The initial peripheral white blood cell counts ranged from 3,280 to 35,000 per cubic millimeter, with approximately half of the counts ranging between 5,000 and 10,000 cells per cubic millimeter. Leukopenia was not a common observation and, in general, the differential counts were within the normal range.

Forty-eight patients received antibiotics. Of these, only 26 had polymorphonuclear pleocy-

tosis. The most common antibiotics used were ampicillin or a combination of penicillin and kanamycin. Antibiotic treatment did not seem to alter the course of the aseptic meningitis.

### Viral Isolations and Serology

Specimens from 115 patients were submitted for viral isolation; an enterovirus was isolated from 51 patients (table 5). ECHO 4 was recovered from 31 patients, and Coxsackie B5 from 13 patients. ECHO 9 virus was isolated from four patients, while single isolations of Coxsackie A9, ECHO 6, and Coxsackie B4 accounted for the remainder. In no instance were two different enteroviruses isolated from specimens from the same patient. Of the total 63 enterovirus isolates, 54 percent were found in the stool, 25 percent in throat swab specimens, and 19 percent in the spinal fluid; in numerous instances, isolations were made from more than one source.

**Table 3. Clinical symptoms in 202 cases of aseptic meningitis, Baltimore, Md., July-October 1967**

Sign or symptom	202 cases reviewed		31 cases with ECHO 4 isolated		13 cases with Coxsackie B5 isolated	
	Number	Percent	Number	Percent	Number	Percent
Fever.....	190	94.1	31	100.0	12	92.3
Headache.....	168	83.2	29	93.5	10	76.9
Nausea or vomiting.....	124	61.3	14	45.2	8	61.5
Anorexia.....	74	36.6	12	38.7	9	69.2
Stiff neck.....	124	61.3	19	61.3	7	53.8
Upper respiratory symptoms.....	36	17.8	8	25.8	3	23.8
Photophobia.....	25	11.8	9	29.0	3	23.8
Myalgia.....	16	7.9	2	6.5	1	7.7

**Table 4. Spinal fluid pleocytosis in 202 cases of aseptic meningitis, Baltimore, Md., July-October 1967**

White blood cells per cubic millimeter	Cases reviewed		ECHO 4 isolated		Coxsackie B5 isolated	
	Number	Percent	Number	Percent	Number	Percent
Less than 10.....	6	2.9	2	6.5	0	0
10-49.....	38	18.8	6	19.3	1	7.7
50-99.....	37	18.3	7	22.6	1	7.7
100-499.....	64	31.6	10	32.2	2	15.4
500-1,000.....	33	16.3	2	6.5	5	38.5
1,000 and over.....	18	8.7	4	12.9	4	30.7
Unknown <sup>1</sup> .....	6	2.9	0	0	0	0
Total.....	202	99.5	31	100.0	13	100.0

<sup>1</sup> Pleocytosis present, but number of cells unspecified.

<sup>2</sup> Percentages do not add to 100 because of rounding.

In 16 cases in which paired serums were submitted, either ECHO 4 or Coxsackie B5 virus was isolated. Infection by the agent isolated was demonstrated by a fourfold or greater rise in neutralizing antibody titer in 14 cases (87.5 percent). In one case in which Coxsackie B5 was isolated from the stool, a diagnostic serologic rise occurred in response to both Coxsackie B5 and mumps virus.

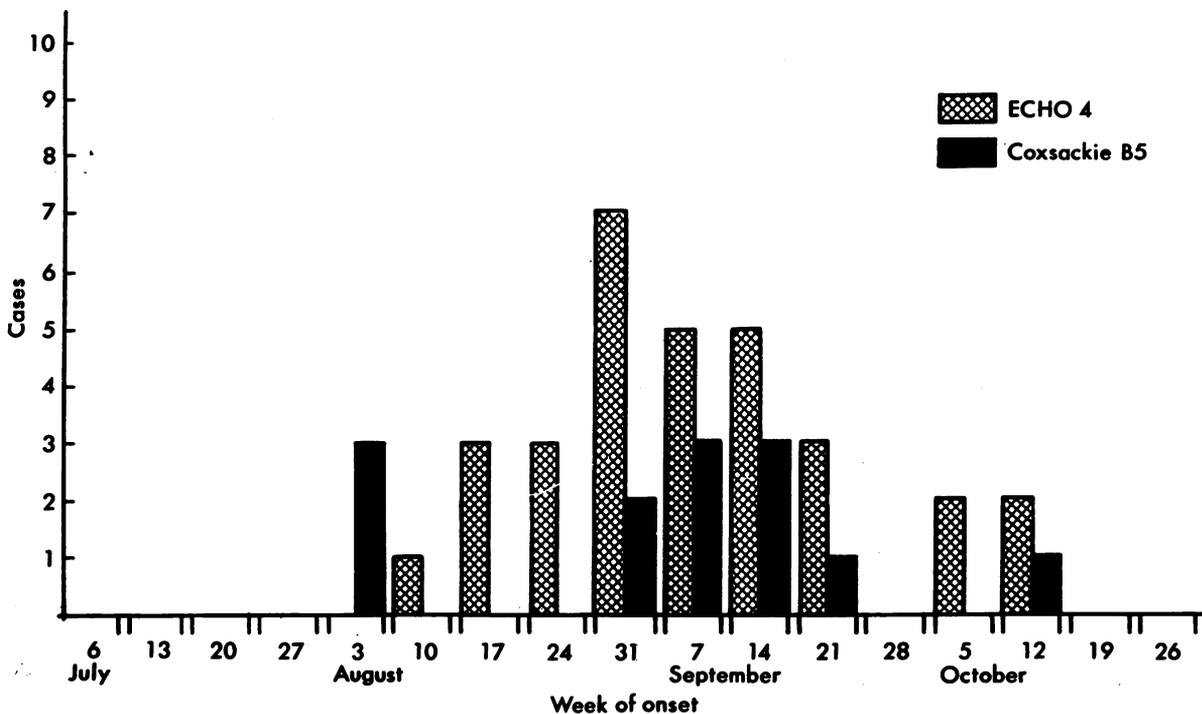
In figure 2, cases in which either ECHO 4 or

Coxsackie B5 was isolated are grouped according to the week of onset of symptoms. Although the numbers are relatively small, the temporal distribution of these cases, as would be expected, is similar to the epidemic curve. Both enteroviruses were present concurrently throughout the community. The cases in which isolations were made were not geographically clustered. While the group of patients from whom ECHO 4 viruses were isolated were slightly older than

**Table 5. Enteroviral isolations and serologic response in 115 cases of aseptic meningitis, Baltimore, Md., July-October 1967**

Enteroviruses	Number of isolations from—				Patients with rise in titer	Patients with a virus implicated	
	85 stool specimens	71 spinal fluid specimens	53 throat specimens	209 specimens submitted		Number	Percent
ECHO 4.....	20	7	10	37	11	31	60.7
Coxsackie B5.....	9	3	6	18	5	13	25.5
ECHO 9.....	2	2	0	4	4	4	7.8
Coxsackie A9.....	1	0	1	2	0	1	2.0
ECHO 6.....	1	0	0	1	0	1	2.0
Coxsackie B4.....	1	0	0	1	1	1	2.0
Total.....	34	12	17	63	21	51	100.1

**Figure 2. Cases of aseptic meningitis in which ECHO 4 or Coxsackie B5 was isolated, by week of onset, Baltimore, Md., July-October 1967**



the total group of patients, the group from whom Coxsackie B5 viruses were isolated were similar in age distribution to the total group. Clinical signs and symptoms in these two groups were similar to those of the entire study population. Isolation of either ECHO 4 or Coxsackie B5 was 1.5 times more frequent in the males.

### Discussion

The epidemic of aseptic meningitis in Baltimore during the summer and early fall of 1967 resembled in many respects other epidemics of viral meningitis described in the literature (4-6, 8). The higher incidence of cases in the younger age group is consistent with habits that are probably less hygienic than those of the general population and that increase the likelihood of fecal-oral contamination and the spread of viruses. It may also reflect less opportunity for prior exposure to the enteroviral agents implicated (9). The higher attack rate for whites 20-24 years old in comparison with the rate for whites 15-19 years, although not statistically significant, may reflect greater contact between young adults and young children. The greater number of reports of illness in nonwhites may be related to the more crowded and less sanitary conditions of the inner city, where many nonwhites live. In addition, nonwhites were selectively included, since most cases for our study were derived from patients of teaching hospitals and clinics. Private physicians are less likely to perform lumbar punctures on patients with mild or equivocal syndromes and, in general, are less likely to report aseptic meningitis.

During the epidemic period, 74 cases of aseptic meningitis were reported in Maryland, outside the city of Baltimore. All these cases were in counties close to Baltimore. Specimens were submitted for 41 of these patients with reported cases. Of 15 enteroviruses of all types isolated from this group, eight were Coxsackie B5 and five were ECHO 9. No ECHO 4 isolations were made. In addition, during the period July-October 1967, enteroviruses were isolated from 42 other Maryland residents who were ill but did not have symptoms of aseptic meningitis. In this group, 22 isolations were of Coxsackie B5 and six were of ECHO 4.

The summer's experience indicates that two enteroviruses were co-dominant during this

period. Statewide, ECHO 4 and Coxsackie B5 were isolated in almost equal numbers from 108 patients with a variety of viral syndromes. In Baltimore, however, ECHO 4 apparently played a more prominent role in the outbreak of aseptic meningitis.

To our knowledge, our report is the first of an outbreak of aseptic meningitis in the United States associated with two dominant enteroviruses, excluding poliovirus. Although Johnson and associates (10) reported an epidemic of central nervous system disease of mixed enteroviral etiology in Hawaii in 1958, two types could not apparently account for the majority of the nonparalytic cases. Hinuma and associates (11) and Nakao and associates (12) reported an outbreak in northern Japan in the summer of 1961 in which Coxsackie B5 and, to a much lesser extent, Coxsackie A9 were isolated. It has been assumed that two or more dominant Coxsackie or ECHO virus types might concurrently be responsible for epidemic aseptic meningitis. Our observations in Baltimore document such an occurrence in the United States.

### Summary

In Baltimore, Md., from July through October 1967, an epidemic of aseptic meningitis occurred in which two enteroviruses, ECHO 4 and Coxsackie B5, were concurrently the dominant agents that were etiologically implicated. A total of 202 cases were reported; the overall attack rate was 22.1 per 100,000 population.

A virus was recovered from 51 patients. The agent was ECHO 4 in 31 cases and Coxsackie B5 in 13 others. Serologic confirmation of infection by the agent isolated—ECHO 4 or Coxsackie B5—was obtained for 87.5 percent of the patients tested. The confirmed cases appeared to be generally representative of the 202 cases reviewed clinically.

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**Tearsheet Requests**

National Communicable Disease Center, Atlanta, Ga. 30333. Attention: Epidemiology Program



**Beware the Wind.** Order No. M-1707-X. Motion picture, 16 mm., color, sound, 22 minutes, 1967. Not cleared for television. Produced by Airlie House for George Washington University, Washington, D.C.

**SUMMARY:** Underscores the threat of worldwide air pollution by showing the origins and evolution of dirty air in American cities and in the capitals of Europe. Shows principal sources of pollution, including industrial operations, burning dumps, motor vehicles, and combustion of fossil fuels. Describes the effects of air pollution on animals, people, and property, showing striking shots of large cities under visible pollution. Suggests ways of applying available technology to clean up the air

through efforts of a concerned citizenry. Narrated by Robert Preston. (Not available for purchase.)

**On a Clear Day You Can Almost See Terminal Tower.** Order No. M-1712-X. Motion picture, 16 mm., color, sound, 22 minutes, 1968. Television clearance must be obtained from William Leonard, WKYC-TV, Cleveland, Ohio. Produced by WKYC-TV (Montage), Cleveland.

**SUMMARY:** Spotlights the problem of air pollution by contrasting the level of pollution known by townspeople of Cleveland, Tenn., with that of Cleveland, Ohio. Shows the smog-laden air of Cleveland, Ohio, and studies the city's air quality problem. Presents the principal sources of Cleveland's air problem and their impact on city life through interviews with experts and concerned laymen who describe some effects of living in a polluted atmosphere. Stresses urgent need for taking preventive action. (Not available for purchase.)

**Beware of Ill Winds.** Order No. F-1745-X. Filmstrip, 39 frames, silent, color, 35 mm., and accompanying manual, 1969. Cleared for television. Produced by Sophisticate Film Corp., Elmont, N.Y., with the assistance of the National Air Pollution Control Administration.

**SUMMARY:** Describes the regional approach to control of air pollution under provisions of the Federal Air Quality Act and discusses the role of public hearings conducted prior to a State's adoption of air quality standards. Accompanied by a manual, the filmstrip shows effective scenes of smog-covered cities and is especially recommended for viewing by community action-oriented groups.

**AVAILABLE:** All three films on free short-term loan from National Medical Audiovisual Center (Annex) Station K, Atlanta, Ga. 30324. Purchase "Beware of Ill Winds" from Sophisticate Film Corporation, P.O. Box 70, Meacham Branch, Elmont, N.Y. 11003.